

272. The isoform of claim 271 comprising SEQ ID: 16.

273. The isoform variant of claim 271 comprising SEQ ID NO: 18 or 20.

274. A nucleic acid encoding a polypeptide according to claim 270.

275. An eukaryotic cell comprising a nucleic acids of claim 274.

276. An eukaryotic cell comprising a polypeptide of claim 270.

277. An eukaryotic cell according to claim 275 that is a mammalian cell.

278. A mammalian cell according to claim 277, selected from the group consisting of HEK293 and Neuro2a.

279. A method according to claim 187 in which the determining or measuring step comprises measuring the amount of amyloid beta-peptide released into growth medium of the cell and/or the amount of CTF99 fragments of APP in cell lysates.

280. The method of claim 279 wherein the cell is from a human, rodent or insect cell line.

281. A method for identifying agents that modulate the activity of human Asp1 aspartyl protease (Hu-Asp1), comprising the steps of:

- (a) contacting amyloid precursor protein (APP) and a Hu-Asp1 polypeptide in the presence and absence of the test agent;
- (b) determining the APP processing activity of the polypeptide in the presence and absence of the test agent; and
- (c) comparing the APP processing activity of the polypeptide in the presence of the test agent to the activity in the absence of the test agent to identify an agent that modulates

the APP processing activity of the polypeptide, wherein a modulator that is an Asp1 inhibitor reduces such cleavage and a modulator that is a Asp1 agonist increases such cleavage.

282. A method according to claim 281 wherein the polypeptide comprises an amino acid sequence at least 95% identical to a sequence comprising the amino acid sequence of SEQ ID NO: 2.

283. A method according to claim 281, wherein the polypeptide is a recombinant polypeptide purified and isolated from a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide.

284. A method according to claim 281, wherein the polypeptide is expressed in a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide, wherein the contacting comprises growing the cell in the presence and absence of the test agent, and wherein the determining step comprises measuring APP processing activity of the cell.

285. A method according to claim 284, wherein the determining step comprises measuring the production of amyloid beta peptide by the cell in the presence and absence of the test agent.

286. A method according to claim 284, wherein the cell is a human embryonic kidney cell line 293 (HEK293) cell.

287. A method according to claim 283 wherein the nucleotide sequence is selected from the group consisting of

(a) a nucleotide sequence encoding the Hu-Asp1 amino acid sequence set forth in SEQ ID NO: 1;

(b) a nucleotide sequence encoding a fragment of Hu-Asp1 (SEQ ID NO: 1), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp1

(c) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to a Hu-Asp1-encoding polynucleotide having the sequence set forth in SEQ ID NO: 1.

288. A method according to claim 284, wherein the cell comprises a vector that comprises the polynucleotide.

289. A method according to claim 281, wherein the APP comprises the Swedish mutation (K→N, M→L) adjacent to the  $\beta$ -secretase processing site.

290. A method according to claim 281, wherein the APP further comprises a carboxy-terminal di-lysine.

291. A method according to claim 281, wherein the test agent is an inhibitor.

292. A method according to claim 281, wherein the test agent is an agonist.

293. A method according to claim 281, further comprising a step of treating Alzheimer's Disease with an agent identified as an modulator of Hu-Asp1 according to steps (a)-(c).

294. A method according to claim 281, further comprising a step of making a medicament for the treatment of Alzheimer's Disease with a test agent identified as an inhibitor according to steps (a)-(c).

295. A. method of reducing cellular production of amyloid beta ( $A\beta$ ) from amyloid precursor protein (APP), comprising step of transforming or transfecting cells with an anti-sense reagent capable of reducing Asp1 polypeptide production by reducing Asp1 transcription or translation in the cells, wherein reduced Asp1 polypeptide production in the cells correlates with reduced cellular processing of APP into  $A\beta$ .